UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,863	11/03/2003	Balaram Ghosh	C261 1030.1	9355

26158 7590 01/26/2005

WOMBLE CARLYLE SANDRIDGE & RICE, PLLC
P.O. BOX 7037
ATLANTA, GA 30357-0037

EXAMINER	
FLOOD, MICHELE C	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,863	GHOSH ET AL.	
	Examiner	Art Unit	
	Michele Flood	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of the receipt and entry of the amendment filed on October 25, 2004.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-13 are under examination.

Specification

The disclosure is objected to because throughout the specification boxes, which appear to represent omitted subject matter, are present. Correction is required.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 9-11 as amended remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Newly applied aw necessitated by amendment.

The metes and bounds of Claims 9-11 are rendered unclear by the phrase "administered in an amount in the range of 0.1 to 10 mg/kg of body weight" because it is uncertain as to what the subject matter of the body weight pertains to. The lack of clarity renders the claims ambiguous.

Claims 9-11 recite the limitation "the range" in line 2. There is insufficient antecedent basis for this limitation in the claims. Applicant may overcome the rejection by replacing "the" with a.

Claim Rejections - 35 USC § 102

Claims 1-10 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Aoyama et al. (N). The rejection stands for the reasons set forth in the previous Office action and for the reasons set forth below.

Applicant argues that the cited reference fails to anticipate the claimed subject matter because the *Perilla* seed extract taught by Aoyama contains luteolin and additional compounds. Applicant also argues that Aoyama does not teach what amount of luteolin is actually present in the disclosed extract. Finally, Applicant argues, "In fact, the inventor evidently admits that the composition of the disclosed extract may vary"; and, that the apigenin, chrysoeriol, luteolin and rosmarinic acid are usually contained in the alcoholic extract. Thus, Applicant concludes that the cited reference does not teach any predicted therapeutic amount of any single compound, with particular regard to luteolin, to provide an *in vivo* method for the prevention and/or treatment of asthma in animals comprising the administration of a therapeutically effective dose of luteolin, as instantly claimed. However, Applicant's arguments are not persuasive because Aoyama teaches a method of preventing and/or treating asthma in animals comprising orally administering an effective amount of an alcoholic extract obtained from the *Perilla* seed, which comprises luteolin. Aoyama teaches the reference extract as a histamine

release inhibitor, which is extremely good in action of inhibiting the release of histamine or the development of asthmatic features comprising Early Airway Response (EAR). In [0027], Aoyama teaches administering 0.5-3000 mg/day of the reference extract or 0.3 to 15% weight percent or 0.01-10 weight percent to a patient in need thereof of treatment. Furthermore, Aoyama expressly teaches each of apigenin, chrysoeriol, luteolin and rosmarinic acid as histamine release inhibitors, as well as *Perilla* seed alcohol extracts containing the aforementioned compounds and an EtOAc fraction of *Perilla* seed extract as inhibitors of histamine release, which are useful in the prevention and/or treatment of allergic disease conditions, such as asthma.

Although Applicant argues that it is unclear as to what amount of luteolin comprises the referenced *Perilla* seed extract, Aoyama expressly teaches that the bioactive compounds contained in the disclosed *Perilla* seed extract can be concentrated, condensed or isolated from the plant seed extract, in [0020] through [0023]. Aoyama also teaches that while the referenced extracts are considered as histamine release inhibitors, refining of the active principle compounds contained therein the extracts can be isolated and that fractions with the highest activity can be collected and used as histamine release inhibitors for treatments or prophylaxis of allergic diseases, such as asthma. In [0031], Aoyama teaches a method of isolating luteolin from *Perilla* seed extract. Hence, the method of treatment taught by Aoyama is not only directed to the administration of effective amounts of *Perilla* seed extract or fractions thereof comprising luteolin but also the administration of effective amounts of each of the individual compounds contained therein (including luteolin) to provide the

claimed beneficial functional effect for the claim-designated disease condition. *See* [0010], wherein Aoyama expressly teaches that each of apigenin, chrysoeriol, luteolin and rosmarinic acid may be efficiently extracted from the seed extract and used in the making of therapeutic preparations for oral administration. Furthermore, Aoyama teaches the effective dose range amounts of the histamine release inhibitors for the making of oral pharmaceuticals to be administered to patients in [0027]. In [0029], Aoyama expressly teaches that the referenced histamine isolation inhibitors can substantially reduce an allergic response, such as cellular degranulation (an asthmatic feature of Late Airway Response). For instance, Aoyama teaches, "Therefore, the histamine isolation inhibitor of this invention can treat or prevent effectively the pollinosis which is many symptoms of I-beam allergy, asthma, dry grass heat, rhinitis, urticaria, a drug allergy, etc. Moreover, it becomes possible to prevent allergy in an every day life and to improve a body easily with the allergy prevention external preparations and allergy prevention food containing the histamine isolation inhibitor of this invention."

Applicant argues that the Examiner merely speculates that the method taught by Aoyama prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response (LAR) because nowhere in the referenced teachings does Aoyama provide any support for this conclusion. Applicant's argument is unpersuasive because Aoyama clearly teaches that the administration of the referenced compounds, including luteolin, and extracts or fractions thereof comprising luteolin inhibit the release of histamine, which is a symptomatic developmental feature of EAR; and, as set forth immediately above, Aoyama clearly teaches that the

referenced histamine isolation inhibitors substantially reduce cellular degranulation, which is a symptomatic developmental feature of LAR. Moreover, in [0002] - [0003], Aoyama clearly describes the progressive biomechanisms that lead to the development of allergic responses in allergic disease, such as asthma, and expressly teaches that by controlling or suppressing the release of histamine, one may also prevent symptoms of LAR, *e.g.,* the production of mast cells and IgE. Since, the administration of effective amounts of the compositions taught by Aoyama inhibits the release of histamine, the method of treatment taught by Aoyama would indeed prevent the development of asthmatic features comprising both EAR and LAR.

Finally, while Applicant may continue to argue that Aoyama does not expressly teach that the referenced method of treatment prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, or any of the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, or wherein luteolin inhibits airway constriction or airway hyperactivity, *per se*. However, the method of treatment taught by Aoyama comprises the oral administration of the same ingredient in the same amounts to provide the same beneficial functional effect for the prevention of asthma in patients in need thereof of such treatment. Therefore, the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and

the inhibition of airway constriction and airway hyperactivity are inherent to the method of treatment taught by Aoyama.

The reference anticipates the claimed subject matter.

Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang (U). Newly applied.

Wang teaches a method of orally administering an effective amount of luteolin obtained from plant sources (120 mg/day p.o.) for 10 days to patients with bronchitis. On page 148, Column 2, under "*Clinical Studies*", Wang teaches, "The major symptoms of chronic bronchitis, including cough, asthma, sputum and wheezing, were effectively alleviated with luteolin treatment (Table VI). No liver, cardiac or renal toxicity was reported." Table VI further indicates a rate of 93.3% complete remission of asthma symptoms in bronchitis patients treated with luteolin. Wang does not expressly teach that the referenced method of treatment prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, or any of the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, or wherein luteolin inhibits airway constriction or airway hyperactivity, *per se*. However, the method of treatment taught by Wang comprises the oral administration of the same ingredient in the same amounts to provide the same beneficial functional effect for the prevention of asthma in patients in need thereof of such treatment. Therefore, the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response

(EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level and the inhibition of airway constriction and airway hyperactivity are inherent to the method of treatment taught by Wang.

The reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

Claims 1-13 are rejected under 35 U.S.C. 102(b) as anticipated by Aoyama et al. (N) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Aoyama et al. (N) (U) in view of Nagai (V), Park et al. (W), Kimata et al. (X) and Yamamoto et al. (U1). Newly applied.

The teachings of Aoyama were set forth above.

The claims are drawn to a method of preventing and/or treating asthma in animals including humans comprising administering a therapeutically effective dose of luteolin; wherein the method shows no side effects; wherein the luteolin is administered orally; wherein the development of Early Airway Response and Late Airway Response are prevented; wherein levels of IFN-gamma, IL-5, IL-4 and IgE are modified to a normal level; wherein the duration of administering luteolin ranges between 5 to 10 days; and, wherein luteolin inhibits airway constriction and airway hyperactivity.

Aoyama teaches a method of preventing and/or treating asthma in animals comprising orally administering an effective amount of an alcoholic extract obtained from the *Perilla* seed, which comprises luteolin. Aoyama teaches the reference extract

as a histamine release inhibitor, which is extremely good in action of inhibiting the release of histamine or the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response (LAR). Furthermore, Aoyama expressly teaches each of apigenin, chrysoeriol, luteolin and rosmarinic acid as histamine release inhibitors, as well as *Perilla* seed alcohol extracts containing the aforementioned compounds and an EtOAc fraction of *Perilla* seed extract as inhibitors of histamine release, which are useful in the prevention and/or treatment of allergic disease conditions, such as asthma. In [0027], Aoyama teaches administering 0.5-3000 mg/day of the reference extract or 0.3 to 15% weight percent or 0.01-10 weight percent to a patient in need thereof of treatment. Although Aoyama does not expressly teach that the reference method for prophylaxis and/or treatment of asthma in animals comprising administering luteolin encompasses modifying levels of IFN-gamma, IL-5, IL-4 and IgE to a normal level and inhibiting airway constriction and airway hyperactivity, the claimed functional effects are inherent to the method taught by Aoyama since the instantly claimed method is a one-step process of administering a therapeutic dose of luteolin to a patient in need of prevention and/or treatment of asthma, and since the ingredient, the amount of the ingredient, and the route of administration for the delivery of the ingredient are the same as instantly claimed by Applicant. Thus, a method of preventing and/or treating asthma in animals including humans using natural compound luteolin wherein level of IFN-gamma increases to normal level, wherein level of IL-5 decreases to normal level, wherein level of IL-4 decreases to normal level, wherein level of IgE decreases to normal a level, and wherein luteolin inhibits airway constriction and

inhibits airway hyperactivity is inherent to the method taught by Aoyama. The cited reference discloses a method of preventing and/or treating asthma in animals comprising administering an effective amount of luteolin - - which appears to be identical to the presently claimed method, since the method taught by Aoyama prevents and/or treats asthma in animals in need thereof comprising the administration of therapeutic amounts of a composition comprising natural compound luteolin to provide prevention of the development of asthmatic features comprising Early Airway Response and Late Airway Response; and, it is therefore considered to anticipate the claimed method.

In the alternative, even if the claimed method is not identical to the referenced extract with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced method is likely to inherently possess the same characteristics of the claimed method particularly in view of the similar characteristics which they have been shown to share. Thus, the claimed method would have been obvious to those of ordinary skill in the art within the meaning of USC 103. For instance, even if the claimed method of preventing and/or treating asthma in animals is not identical to the method taught by Aoyama with regard to preventing asthmatic features, *i.e.,* EAR and LAR; or modifying the levels of cellular constituents, *i.e.,* IFN-gamma, IL-5 and IL-4, or inhibiting airway constriction or airway hyperactivity; or the duration for the administration of luteolin; or the amount of the luteolin contained therein the referenced *Perilla* seed extract is not in the same amount as instantly claimed by Applicant, it would

have been obvious to one of ordinary skill in the art to modify the method of preventing and/or treating asthma in animals taught by Aoyama by modifying the amounts of the reference composition to be administered and the duration of the amounts of the reference compositions to be administered to an animal in need thereof to provide the instantly claimed method of prophylaxis or treatment of asthma because at the time the invention was made it was known in the art that the administration of luteolin to animals had the claimed beneficial of altering the levels of IFN-gamma, IL-5, IL-4 and IgE provide an anti-asthmatic effect when administered to animals in need thereof, as evidenced by the teachings of Nagai, Park and Kimata; and that the *Perilla* seed extract and fractions thereof comprised effective amounts of luteolin to effect therapeutic functional effects for the prevention and/or treatment of asthma, as evidenced by the teachings of Yamamoto. Firstly, Nagai investigated the effects of an oriental-medical preparation comprising luteolin, *i.e.,* Sho-seiryu-to, and luteolin on bi-phase allergic reactions mediated by IgE. Nagai teaches administering Sho-seiryu-to once only or daily for a week significantly inhibited both immediate (Early Airway Response, EAR) and late phase reactions (Late Airway Response, LAR) in mice sensitized with anti-DNP monoclonal IgE antibodies and DNP antigen. For example, Nagai teaches, "In immediate-phase instances, Sho-seiryu-to is thought to have effected inhibition by antagonistic operations against mediators, such as histamines released from mast cells. In late-phase cases, it is thought to have inhibited by suppressing the production and operation of cytokines [such] as TNF-alpha." Similarly, Nagai teaches that administration of small quantities of luteolin demonstrated significant inhibitory effects

on both immediate- and late-phase reaction, as well as, the release of histamine. Secondly, Park teaches luteolin obtained from *Kummerowia striata* as a dose-dependent inhibitor of Il-5. *See* Figure 1 on page 458. On page 458, Column 2, lines 16-19, Park further teaches, "An anti-Il-5 monoclonal antibody was reported to inhibit airway infiltration of eosinophils and decrease bronchial hypersensitivity in atopic animal models [citations omitted]." Thirdly, Kimata teaches treating human cultured mast cells sensitized with IgE with luteolin before challenge with antihuman IgE inhibited the release of histamine, leukotrienes, prostaglandin D2, and granulocyte macrophage-colony stimulating factor in a concentration-dependent manner. Fourthly, Yamamoto teaches a method of preparing a *Perilla* seed extract and the isolation and identification of the active components that is identical to the making of the *Perilla* seed extract taught by Aoyama, on pages 862-863, under "*MATERIAL AND METHODS*". In Figure 1, Yamamoto teaches that the extraction and isolation of active compounds from defatted *Perilla* seed extract yields 240 mg of luteolin. Thus, the amount of the luteolin comprising the *Perilla* seed extract taught by Aoyama is not unknown, as argued by Applicant. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the method of prophylaxis and/or treatment taught by Aoyama by adjusting the therapeutic amounts of the reference compositions comprising luteolin to be administered and the duration of the amounts of the reference compositions to be administered to an animal in need thereof to provide the instantly claimed method of prophylaxis or treatment of asthma because at the time the invention was made it was

known in the art that the administration of luteolin to animals had the claimed beneficial of altering the levels of the claim-designated components which are well-known mediators in the development of asthma (as readily admitted by Applicant on page 1, lines 23-28 of the present application) to provide the claimed method of prophylaxis and/or treatment asthma in animals because Aoyama teaches a method of treating asthma comprising administering therapeutic effective amounts of luteolin obtained from natural plant sources; and, Nagai, Park and Kimata teach that therapeutic effective amounts of luteolin have the beneficial effect of mediating the levels of cellular components known to effect the development of asthmatic features; and, on page 864, Column 2, lines 20-24, Yamamoto teaches that ethanolic extracts of defatted *Perilla* seed prepared by the same method as taught by Aoyama contains a large quantity of luteolin and has the potential to play a role in the regulation of allergic diseases.

Thus, it would have been a matter of judicious selection to one of ordinary skill in the art to modify the amounts and the duration of the amounts of luteolin administered to a patient in need thereof to provide a therapeutically effective dose of luteolin to provide an immunomodulatory result effect variable since at the time the invention was made it was known in the art of medicine that the claim-designated limitations were known biochemical and biological mechanisms affecting the development or reduction of asthmatic symptoms and since luteolin was known to exhibit therapeutic activity in the treatment thereof. The claimed invention is no more than the routine optimization of a result effect variable. Thus, the claimed methods would have been obvious to those of ordinary skill in the art within the meaning of USC 103.

The United States Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether on not Applicants' method differs and, if so, to what extent, from that discussed in the references. Therefore, with the showing of the references, the burden of establishing non-obviousness by objective evidence is shifted to Applicants.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Accordingly, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated by the reference, especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1-13 are rejected under 35 U.S.C. 102(b) as anticipated by Wang (U) or, in the alternative, under 35 U.S.C. 103(a) as obvious over Wang al. (U) in view of Nagai (V), Park et al. (W), and Kimata et al. (X).

Applicant's claimed invention was set forth above.

The teachings of Wang were set forth above.

The claims are drawn to a method of preventing and/or treating asthma in animals including humans comprising administering a therapeutically effective dose of luteolin; wherein the method shows no side effects; wherein the luteolin is administered orally; wherein the development of Early Airway Response and Late Airway Response are prevented; wherein levels of IFN-gamma, IL-5, IL-4 and IgE are modified to a

normal level; wherein the duration of administering luteolin ranges between 5 to 10 days; and, wherein luteolin inhibits airway constriction and airway hyperactivity.

Wang teaches a method of orally administering an effective amount of luteolin obtained from plant sources (120 mg/day p.o.) for 10 days to patients with bronchitis. On page 148, Column 2, under "*Clinical Studies*", Wang teaches, "The major symptoms of chronic bronchitis, including cough, asthma, sputum and wheezing, were effectively alleviated with luteolin treatment (Table VI). No liver, cardiac or renal toxicity was reported." Table VI further indicates a rate of 93.3% complete remission of asthma symptoms in bronchitis patients treated with luteolin. Wang does not expressly teach that the referenced method of treatment prevents development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, or any of the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, or the inhibition of airway constriction and airway hyperactivity, *per se*. However, the method of treatment taught by Wang comprises the oral administration of the same ingredient in the same amounts to provide the same beneficial functional effect for the prevention of asthma in patients in need thereof of such treatment. Therefore, the claimed functional effects for the prevention of the development of asthmatic features comprising Early Airway Response (EAR) and Late Airway Response, and the claimed functional effects of increasing IFN-gamma to a normal level and decreasing each of IL-5, IL-4 or IgE to a normal level, and the inhibition of airway constriction and airway hyperactivity are inherent to the method of treatment taught by Wang. Thus, a method of preventing and/or treating asthma in

animals including humans using natural compound luteolin wherein the level of IFN-gamma increases to normal level, wherein the level of IL-5 decreases to normal level, wherein the level of IL-4 decreases to normal level and wherein the level of IgE decreases to normal a level, wherein airway constriction is inhibited, and wherein airway hyperactivity is inhibited are inherent to the method taught by Wang. The cited reference discloses a method of preventing and/or treating asthma in animals comprising administering an effective amount of luteolin - - which appears to be identical to the presently claimed methods, since the method taught by Wang prevents and/or treats asthma in animals in need thereof comprising the administration of therapeutic amounts of a composition comprising natural compound luteolin; and, it is therefore considered to anticipate the claimed method.

In the alternative, even if the claimed method is not identical to the referenced extract with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are considered to be so slight that the referenced method is likely to inherently possess the same characteristics of the claimed method particularly in view of the similar characteristics which they have been shown to share. Thus, the claimed method would have been obvious to those of ordinary skill in the art within the meaning of USC 103. For instance, even if the claimed method of preventing and/or treating asthma in animals is not identical to the method taught by Wang with regard to preventing asthmatic features, *i.e.,* EAR and LA; or modifying the levels of cellular constituents, *i.e.,* IFN-gamma, IL-5 and IL-4, or inhibiting airway constriction or airway hyperactivity; or the duration for the

administration of luteolin, it would have been obvious to one of ordinary skill in the art to modify the method of preventing and/or treating asthma in animals taught by Wang by modifying the amounts of the reference composition to be administered and the duration of the amounts of the reference compositions to be administered to an animal in need thereof to provide the instantly claimed method of prophylaxis or treatment of asthma because at the time the invention was made it was known in the art that the administration of luteolin to animals had the claimed beneficial of altering the levels of IFN-gamma, IL-5, IL-4 and IgE thus provide an anti-asthmatic effect when administered to animals in need thereof, as evidenced by the teachings of Nagai, Park and Kimata. Firstly, Nagai investigated the effects of an oriental-medical preparation comprising luteolin, *i.e.,* Sho-seiryu-to, and luteolin on bi-phase allergic reactions mediated by IgE. Nagai teaches administering Sho-seiryu-to once only or daily for a week significantly inhibited both immediate (Early Airway Response, EAR) and late phase reactions (Late Airway Response, LAR) in mice sensitized with anti-DNP monoclonal IgE antibodies and DNP antigen. For example, Nagai teaches, "In immediate-phase instances, Sho-seiryu-to is thought to have effected inhibition by antagonistic operations against mediators, such as histamines released from mast cells. In late-phase cases, it is thought to have inhibited by suppressing the production and operation of cytokines [such] as TNF-alpha." Similarly, Nagai teaches that administration of small quantities of luteolin demonstrated significant inhibitory effects on both immediate- and late-phase reaction, as well as, the release of histamine. Secondly, Park teaches luteolin obtained from *Kummerowia striata* as a dose-dependent inhibitor of Il-5. *See* Figure 1 on page

458. On page 458, Column 2, lines 16-19, Park further teaches, "An anti-Il-5 monoclonal antibody was reported to inhibit airway infiltration of eosinophils and decrease bronchial hypersensitivity in atopic animal models [citations omitted]." Thirdly, Kimata teaches treating human cultured mast cells sensitized with IgE with luteolin before challenge with antihuman IgE inhibited the release of histamine, leukotrienes, prostaglandin D2, and granulocyte macrophage-colony stimulating factor in a concentration-dependent manner. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to modify the method of prophylaxis and/or treatment taught by Wang by adjusting the therapeutic amounts of the reference composition comprising luteolin and the duration of the amounts of the reference compositions administered to an animal in need thereof to provide the instantly claimed method of prophylaxis or treatment of asthma because at the time the invention was made it was known in the art of medicine that the administration of luteolin to animals had the claimed beneficial effect of altering the levels of the claim-designated components which are well-known mediators in the development of asthma (as readily admitted by Applicant on page 1, lines 23-28 of the present application) to provide the claimed method of prophylaxis and/or treatment asthma in animals because Wang teaches a method of treating asthmatic symptoms in patients comprising administering therapeutic effective amounts of luteolin obtained from natural plant sources and luteolin was known in the art to have inhibitory effects against macrophages, have dose-dependent inhibitory effects on interleukin (IL)-5 activity and to promote eosinophil growth and survival known to play

an important role in eosinophilia-associated allergic inflammation, on page 147, Column 1, lines 4-21; and, Nagai, Park and Kimata teach that therapeutic effective amounts of luteolin have the beneficial effect of mediating the levels of cellular components known to effect the development of asthmatic features. Thus, it would have been a matter of judicious selection to one of ordinary skill in the art to modify the amounts and the duration of the amounts of luteolin administered to a patient in need thereof to provide a therapeutically effective dose of luteolin to provide an immunomodulatory result effect variable since at the time the invention was made it was known in the art of medicine that the claim-designated limitations were known biochemical and biological mechanisms affecting the development or reduction of asthmatic symptoms and since luteolin was known to exhibit therapeutic activity in the treatment thereof. The claimed invention is no more than the routine optimization of a result effect variable. Thus, the claimed methods would have been obvious to those of ordinary skill in the art within the meaning of USC 103.

The United States Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether on not Applicants' method differs and, if so, to what extent, from that discussed in the references. Therefore, with the showing of the references, the burden of establishing non-obviousness by objective evidence is shifted to Applicants.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Accordingly, the claimed invention as a whole was at least *prima facie*

obvious, if not anticipated by the reference, especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is 571-272-0964. The examiner can normally be reached on 7:00 am - 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele C. Flood.

MICHELE FLOOD
PATENT EXAMINER
Michele Flood
January 18, 2005